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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,314	04/29/2005	Gehua Wang	85043-302	1562

7590 11/28/2008

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EXAMINER	
SHAHNAN SHAH, KHATOL S	
ART UNIT	PAPER NUMBER
1645	
MAIL DATE	DELIVERY MODE
11/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,314	WANG ET AL.	
	Examiner	Art Unit	
	Khatol S. Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

1. The amendment filed 8/12/2008 has been entered into the record. Claims 1-4 have been cancelled. Claim 5 has been amended.

Status of Claims

2. Claims 5 is pending and under examination.

Rejections Maintained

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Rejection of claim 5 rejected under 35 U.S.C. 102(b), made in paragraph 5 of the office action mailed 04/01/2008 is maintained.

The rejection was stated below:

> Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Pass et al. (Journal of Clinical Microbiology vo1.38, no. 5, pp. 2001-2004, May 2000) prior art of record applicants' International Search Report submitted 7/23/2004.

Claim 5 is drawn to a method for detecting the presence of E.coli virulence related genes in sample by multiplex PCR , i.e. adding the sample to a amplification mixture including at least one pair of primers selected from the group consisting of at least 15 contiguous nucleotides of SEQ ID NO 1 , 2, 5 and 6.

Pass et al. teach a method for detecting the presence of E.coli virulence related genes in sample by multiplex PCR, i.e. adding the sample to an amplification mixture including at least one pair of primers selected from the group consisting of at least 15 contiguous nucleotides of SEQ ID NO 1, 2, 5 and 6. Pass et al. also teach primers for amplifying VT1, VT2, VT2e and other genes of E.coli (see abstract, page 2001 and table 2). The SEQ ID NO: 1, 2, 5 and 6 or VT1-a, VT1-b, VT2-a and VT2-b will be

inherent in the genes and primers taught by Pass et al. Claim 5 is drawn to a method for detecting the presence of E.coli virulence related genes in sample by multiplex PCR, i.e. adding the sample to a amplification mixture including at least one pair of primers selected from the group consisting of at least 15 contiguous nucleotides of SEQ ID NO 1, 2, 5 and 6. SEQ ID NO: 1, 2, 5 and 6 are defined as VT1-a, VT1-b, VT2-a and VT2-b. Pass et al. also teach primers for amplifying genes VT1, VT2, therefore SEQ ID NO: 1, 2, 5 and 6 as VT1-a, VT1-b, VT2-a and VT2-b. are included in the total sequence of these genes and therefore will be inherent in the genes and primers taught by Pass et al.

Applicants' arguments of 08/11/2008 have been fully considered but they are not persuasive.

Applicant argues that:

- Specifically, in both cases, the office action states that the claimed primers are 'inherent in the genes and primers' taught by the prior art. Applicants respectfully request that the examiner reconsider these rejections. Specifically, the primers described above have been selected based on their ability to give clean and consistent results when used with other primer pairs within the multiplex system. As discussed above, claim 5 has been amended to incorporate the multiplex aspect of the invention, specifically, the ability to combine the primers of claim 5 with primers used for the amplification of other virulence genes.

- Specifically, the primers described in the instant application can be used to detect stxl, stx2, stx2c, stc2d, stx2e, stx2f, eaeA, EHEC hlyA, rfbeO157, filcH7 and 16s rRNA by multiplex PCR as discussed in the application as filed and in claim 5. The primers are very specific for the detection of these genes without the use of restriction enzymes. The use of other primer combinations aside from the VT1 and VT2 primer pairs described in claim 5 with the other primers may lead to non-specific PCR cross reactions when used in a multiplex assay, rendering the assay useless and non-informative. Accordingly, applicants believe that the VT-1 and VT-2 primers described by Pass et al. and Ganon et al. as multiplex primers

can not be used in place of the primers described in the instant application, that is, cannot be used in combination with the disclosed primer pairs for the detection of at least one of the following *Escherichia coli* virulence-related genes selected from the group consisting of: eaeA, EHEC-HlyA, Stx2c, Stx2d, Stx2e, rfbE and flic.

- Applicants respectfully note that many primers detecting VT-1 and VT- 2 have been published since the late 1980s or early 1990s. However, these primers can not just be simply integrated into a multiplex system due to a variety of unpredictable factors including but by no means limited to primer-dimer formations, primer-sequence secondary structure anomalies, PCR reaction conditions, primer-primer interference phenomena, PCR amplicon size variations and other problematic issues which may result in the product being unreliable, unpredictable or irreproducible. In essence, PCR reactions often produce unexpected and/or unexplainable results and the selection of primers for use in a multiplex system such as described in the instant application and amended claims is not always straight-forward and accordingly applicants maintain that the selection of such primers cannot be 'inherent'.

- Applicants further note that one primer pair is derived from the B-subunit and is highly specific for VT-2. In contrast, for example, those of Pass et al. are derived from the A-subunit and will cross react with other VT-2 subtypes and therefore cannot identify each separately without multiple digestions and PCR steps. In this respect the primers taught by Pass cannot both detect and separate the different virulent subtypes of this pathogen. To achieve this, a further step and additional primers would need to be used.

In re to applicants arguments claim 5 is drawn to a method for detecting the presence of E.coli virulence related genes in sample by multiplex PCR, i.e. adding the sample to a amplification mixture including at least one pair of primers selected from the

group consisting of SEQ ID NO 1, 2, 5 and 6. SEQ ID NO: 1, 2, 5 and 6 and primer pair for the detection of at least E.coli virulence related genes selected from eaeA and flic. Pass et al. teach such method as mentioned above. Pass et al. teach eaeA primer see pages 2001-2002 , figures 1-2 and tables 1 and 2. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., A and B subunits) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

5. Rejection of claim 5 rejected under 35 U.S.C. 102(b), made in paragraph 6 of the office action mailed 04/01/2008 is maintained.

Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Gannon et al. (Journal of Clinical Microbiology vo1.35, no. 3, pp. 656-662, March 1997) prior art of record applicants' International Search Report submitted 7/23/2004.

The rejection was stated below:

Claim 5 is drawn to a method for detecting the presence of E.coli virulence related genes in sample by multiplex PCR , i.e. adding the sample to a amplification mixture including at least one pair of primers selected from the group consisting of at least 15 contiguous nucleotides of SEQ ID NO 1 , 2, 5 and 6.

Gannon et al. teach a method for detecting the presence of E.coli virulence related genes in sample by multiplex PCR, i.e. adding the sample to a amplification mixture including at least one pair of primers selected from the group consisting of at least 15 contiguous nucleotides of SEQ ID NO 1, 2, 5 and 6.Gannon et al. also teach primers for amplifying VT1, VT2, VT2e and other genes of E.coli (see abstract, and table 1). The SEQ ID NO: 1, 2, 5 and 6 or VT1-a, VT1-b, VT2-a and VT2-b will be inherent in the genes and primers taught by Gannon et al.

Note: Applicants specification pages 10 and 11 identify SEQ ID NO: 1, 2, 5 and 6 as VT1-a, VT1-b, VT2-a and VT2-b.

Applicants' arguments of 08/11/2008 have been fully considered but they are not persuasive.

Applicant argues that:

- Specifically, in both cases, the office action states that the claimed primers are 'inherent in the genes and primers' taught by the prior art. Applicants respectfully request that the examiner reconsider these rejections. Specifically, the primers described above have been selected based on their ability to give clean and consistent results when used with other primer pairs within the multiplex system. As discussed above, claim 5 has been amended to incorporate the multiplex aspect of the invention, specifically, the ability to combine the primers of claim 5 with primers used for the amplification of other virulence genes.

- Specifically, the primers described in the instant application can be used to detect stxl, stx2, stx2c, stc2d, stx2e, stx2f, eaeA, EHEC hlyA, rfbeO157, filcH7 and 16s rRNA by multiplex PCR as discussed in the application as filed and in claim 5. The primers are very specific for the detection of these genes without the use of restriction enzymes. The use of other primer combinations aside from the VT1 and VT2 primer pairs described in claim 5 with the other primers may lead to non-specific PCR cross reactions when used in a multiplex assay, rendering the assay useless and non-informative. Accordingly, applicants believe that the VT-1 and VT-2 primers described by Pass et al. and Ganon et al. as multiplex primers can not be used in place of the primers described in the instant application, that is, cannot be used in combination with the disclosed primer pairs for the detection of at least one of the following *Escherichia coli* virulence-related genes selected from the group consisting of: eaeA, EHEC-HlyA, Stx2c, Stx2d, Stx2e, rfbE and flic.

- Applicants respectfully note that many primers detecting VT-1 and VT- 2 have been published since the late 1980s or early 1990s. However, these primers can not just be simply integrated into a multiplex system due to a variety of unpredictable factors including but by no means limited to primer-dimer formations, primer-sequence secondary structure anomalies, PCR reaction conditions, primer-primer interference phenomena, PCR amplicon size variations and other problematic issues which may result in the product being unreliable, unpredictable or irreproducible. In essence, PCR reactions often produce unexpected and/or unexplainable results and the selection of primers for use in a multiplex system such as described in the instant application and amended claims is not always straight-forward and accordingly applicants maintain that the selection of such primers cannot be 'inherent'.

- Applicants further note that one primer pair is derived from the B-subunit and is highly specific for VT-2. In contrast, for example, those of Pass et al. are derived from the A-subunit and will cross react with other VT-2 subtypes and therefore cannot identify each separately without multiple digestions and PCR steps. In this respect the primers taught by Pass cannot both detect and separate the different virulent subtypes of this pathogen. To achieve this, a further step and additional primers would need to be used.

In re to applicants arguments claim 5 is drawn to a method for detecting the presence of E.coli virulence related genes in sample by multiplex PCR, i.e. adding the sample to a amplification mixture including at least one pair of primers selected from the group consisting of SEQ ID NO 1, 2, 5 and 6. SEQ ID NO: 1, 2, 5 and 6 and primer pair for the detection of at least E.coli virulence related genes selected from eaeA and flic. **6.** et al. teach such method as mentioned above. c al. teach eaeA and flic primers see abstracts, page 658 and tables 2. In response to applicant's argument that the

references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., A and B subunits) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is 571-272-0863. The examiner can normally be reached on Mondays and Wednesdays from 12:30-6:30 PM and Thursdays from 12:30-4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Khatol S Shahnan-Shah/
Examiner, Art Unit 1645
November 20, 2008

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645